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PTO/SB/64 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT ABANDONED UNINTENTIONALLY UNDER 37 CFR 1.137(b)

Docket Number (Optional): 102912-200

First named inventor: LORENZ POELLINGER

Application No.: 09/922,958 Art Unit: 1642

Filed: AUGUST 7, 2001 Examiner: B. FETTEROLF

Title: MECHANISM OF CONDITIONAL REGULATION OF THE HYPOXIA-INDUCIBLE FACTOR-1 BY THE VON HIPPEL-LINDAU TUMOR SUPPRESSOR

Attention: Office of Petitions
Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
FAX (571) 273-8300

NOTE: If information or assistance is needed in completing this form, please contact Petitions Information at (571) 272-3282.

The above-identified application became abandoned for failure to file a timely and proper reply to a notice or action by the United States Patent and Trademark Office. The date of abandonment is the day after the expiration date of the period set for reply in the office notice or action plus an extensions of time actually obtained.

APPLICANT HEREBY PETITIONS FOR REVIVAL OF THIS APPLICATION

NOTE: A grantable petition requires the following items:
(1) Petition fee;
(2) Reply and/or issue fee;
(3) Terminal disclaimer with disclaimer fee - required for all utility and plant applications filed before June 8, 1995; and for all design applications; and
(4) Statement that the entire delay was unintentional.

1.Petition fee

☑ Small entity-fee $ 750.00 (37 CFR 1.17(m)). Applicant claims small entity status. See 37 CFR 1.27.

☐ Other than small entity – fee $ _____ (37 CFR 1.17(m))

2. Reply and/or fee

A. The reply and/or fee to the above-noted Office action in the form of RCE and AMENDMENT TO ACCOMPANY RCE (identify type of reply):

☐ has been filed previously on _____.
☑ is enclosed herewith.

B. The issue fee and publication fee (if applicable) of $ _____.

☐ has been paid previously on _____.
☐ is enclosed herewith.

3. Terminal disclaimer with disclaimer fee

☑ Since this utility/plant application was filed on or after June 8, 1995, no terminal disclaimer is required.

☐ A terminal disclaimer (and disclaimer fee (37 CFR 1.20(d)) of $ _____ for a small entity or $ _____ for other than a small entity) disclaiming the required period of time is enclosed herewith (see PTO/SB/63).

4. STATEMENT: The entire delay in filing the required reply from the due date for the required reply until the filing of a grantable petition under 37 CFR 1.137(b) was unintentional. [NOTE: The United States Patent and Trademark Office may require additional information if there is a question as to whether either the abandonment or the delay in filing a petition under 37 CFR 1.137(b) was unintentional (MPEP 711.03(c), subsections (III)(C) and (D)).]

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Todd E. Garabedian — Signature

14 Nov 2006 — Date

TODD E. GARABEDIAN, Ph.D. — Typed or printed name

39,197 — Registration Number, if applicable

Wiggin and Dana LLP, One CityPlace — Address

(860) 297-3716 — Telephone Number

185 Asylum Street, Hartford, Connecticut 06103 — Address

Enclosures:
☐ Fee Payment
☑ Reply
☐ Terminal Disclaimer Form
☑ Additional sheets containing statements establishing unintentional delay
☑ Other: Return Receipt Postcard

CERTIFICATE OF MAILING OR TRANSMISSION [37 CFR 1.8(a)]

I hereby certify that this correspondence is being:

☑ Deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Mail Stop Petition, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

☐ Transmitted by facsimile on the date shown below to the United States Patent and Trademark Office at (571) 273-8300.

14 Nov 2006 — Date

Todd E. Garabedian — Signature

TODD E. GARABEDIAN, Ph.D. — Typed or printed name of person signing certificate

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Lorenz Poellinger et al.	Docket:	102912-200
Serial No.:	09/922,958	Art Unit:	1642
Filed:	August 7, 2001	Examiner:	B. Fetterolf
Assignee:	AngioGenetics AB		
Title:	MECHANISM OF CONDITIONAL REGULATION OF THE HYPOXIA-INDUCIBLE FACTOR-1 BY THE VON HIPPEL-LINDAU TUMOR SUPPRESSOR PROTEIN		

Certificate of Mailing

Date of Deposit: 14 Nov 2006.
I hereby certify under 37 CFR 1.8(a) that this correspondence (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Signed: Todd E. Garabedian

Name: TODD E. GARABEDIAN

PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT ABANDONED UNINTENTIONALLY UNDER 37 CFR 1.137(b)

Mail Stop Petition
Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

As a supplement to the Statement indicated in Item 4 of the Petition for Revival (PTO Form SB/64) submitted herewith, undersigned attorney provides the following remarks to clarify that the entire delay in the filing of the required reply from the due date for the required reply until the filing of a grantable petition under 37 CFR §1.137(b) was unintentional. Further, the undersigned attorney is submitting this Petition under 37 CFR §1.34 in a representative capacity. New Powers of Attorney will be submitted shortly.

1. On March 3, 2006, a Final Office Action was mailed respecting the above-identified patent application (copy attached).

2. On July 6, 2006, former counsel submitted an amendment in response to the Final official action (copy attached).

3. On August 30, 2006, an Advisory Action was mailed by the USPTO. That Advisory Action did not enter Applicants' amendment submitted on July 6, 2006 (copy attached). Applicants did not make any further submissions respecting this application after August 30, 2006, and the application was unintentionally abandoned on September 5, 2006. Applicants note and reiterate for the record that the mailing date of the Advisory Action was August 30, 2006, and the statutory time period for response ended September 5, 2006[1].

4. On September 14, 2006, the undersigned attorney was requested by former counsel to assume responsibility of this application.

5. On September 18, 2006 the undersigned attorney reviewed the file history for this application on the Public PAIR website and found that the application was abandoned for failure to prosecute the application within the statutory time limit. The undersigned attorney informed Applicant that the application was abandoned and recommended submission of a Petition to Revive Application under 37 CFR §1.137(b) along with a Request for Continued Examination.

7. On October 19, 2006, Applicant instructed the undersigned attorney to proceed as suggested and submit a Petition to Revive under 37 CFR §1.137(b) and a Request for Continued Examination.

8. The undersigned attorney submits that the entire delay in filing the requred reply from the due date for the required reply until the filing of a grantable petition under 37 CFR §1/137(b) was unintentional.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United Stated Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

[1] Technically, the period for response ended on September 3, 2006. However, this was a Sunday, and September 4, 2006, was Labor Day, a Federal Holiday where the USPTO is officially closed.

Applicants claim small entity status.

PLEASE CHARGE THE PETITION FEE, AND ANY OTHER FEES DUE WITH THIS REQUEST AND PETITION TO DEPOSIT ACCOUNT 23-1665.

Respectfully submitted,

Date: 14 NOV 2006

Todd E. Garabedian, Ph.D.
Reg. No. 39,197

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,958	08/07/2001	Lorenz Poellinger	3743/49008	9818

26288 7590 03/03/2006

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STOCKHOLM,
SWEDEN

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,958	POELLINGER ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33 and 35-66* is/are pending in the application.

4a) Of the above claim(s) *1-32, 37-39 amd 43-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33, 35-36 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

Response to the Amendment

The Amendment filed on 12/28/2005 in response to the previous Non-Final Office Action (9/21/2005) is acknowledged and has been entered.

Claims 1-33 and 35-66 are currently pending

Claims 1-32, 37-39 and 43-66 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 33, 35-36 and 40-42 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33 and 35-36 **remain** rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As set forth previously, "an isolated protein according to claim 29" is the isolated polypeptide of Claim 1 comprising an amino acid sequence of SEQ ID NO: 4 and fragments thereof with an altered PYI motif at residues 564-566. In the instant case, claims 33-36 are inclusive of a genus of molecules identified as comprising an amino acid sequence set forth in SEQ ID NO: 4 or any fragments and/or mutants thereof that bind to a genus of target proteins and fragments thereof referred to as "VHL". While claims 40-42 are inclusive of a genus of molecules referred to as having a "PYI motif" or functional fragments thereof and a genus of molecules referred to as

"P564 spanning protein" or functional fragments thereof. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for methods of identifying agents. not all fragments

The specification teaches (page 9, paragraph 0026-0027) that methods for identifying agents of the present invention includes, but is not limited to, polypeptides having at least an amino acid of SEQ ID NO: 5 (minimum N-TAD) or a smaller fragment thereof, SEQ ID NO: 6 (residues 547-575), or described mutants thereof and the VHL protein (SEQ ID NO: 2). With regards to the mutants, the specification teaches (Pages 6-7) that the mutants comprise altered amino acid residues such as; an altered PYI motif at residues 564-566, a ^{564}P, a $^{565\text{-}566}$YI, ^{565}Y, a $^{569\text{-}571}$DDD, ... ect.. The specification further teaches (page 13, paragraph 0042) that additional methods for identifying agents of the invention include, but are not limited to, polypeptides comprising a PYI motif or p564 spanning polypeptide (residues 547-575) or portion thereof. Thus, it appears that a p564 spanning polypeptide consists of the same amino acids as disclosed for SEQ ID NO: 6. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for identifying agents. Therefore, the written description does not commensurate with the full scope of any fragments and/or variants of SEQ ID NO: 4 or any fragments of the VHL protein (SEQ ID NO: 2).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification

provides neither a representative number of molecules that bind VHL nor does it provide a description of structural features that are common to SEQ ID NO: 4. Further, the specification fails to provide a representative number of molecules referred to as VHL along with a description of structural features that are common to the VHL. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of all the fragments of SEQ ID NO: 4 and VHL, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a VHL protein (SEQ ID NO: 2) and two fragments of SEQ ID NO: 4,(SEQ ID NOs: 5 and 6), which comprise the PYI motif and p564 spanning protein, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In response to the rejection, Applicants contend that the claims have been amended which are believed to obviate this rejection.

The amendments and argument have been carefully considered, but are not found persuasive.

With regards to the amendment, the Examiner acknowledges that SEQ I DNO: 2 has been inserted into the currently pending claims. However, the written description only sets forth the amino acid sequence of SEQ ID NO: 2 in combination with binding to the amino acid of SEQ ID NO: 4; and therefore is not commensurate with the full scope of any fragments of SEQ ID NO: 2 which interact with the amino acid sequence of SEQ ID NO: 4.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40-42 remain rejected under 35 U.S.C. 102(b) as being anticipated by Maxwell et al. (Nature 1999; 399: 271-275, IDS).

Maxwell discloses a method of evaluating an antagonist of the PYI motif for VHL-HIF-1 alpha interacting inhibiting efficacy; comprising: determining a reference level of VHL-HIF-1 alpha interacting in a cell or group of cells; administering said antagonist to an equivalent test cell; measuring the level of VHL-HIF-1 alpha interaction in said test cell; and determining said antagonist is efficacious when the measured test level of VHL-HIF-1 alpha interaction is less than the reference level of VHL-HIF-1 alpha interaction (page 273, 1st column, 1st full paragraph to 2nd column). The reference further teaches that the test were done at both normoxic and hypoxic conditions (page 273, 1st column, 1st full paragraph to 2nd column). Thus, while the Maxwell et al. does not specifically state that the inhibitor is an agonist of the PYI motif, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Tanimoto et al. (EMBO 2000; 19: 4298-4309, IDS), the highly conserved core motif, i.e. PYI, of the N-TAD of HIF-1 alpha is critical for interaction with VHL (specifically page 4303, 1st column, 1st full paragraph). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method

steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

In response to this rejection, Applicants contend that while Maxwell et al. discloses a method of evaluating a PYI antagonist, Maxwell fails to disclose the method set forth in the amended claims which relies on SEQ ID NO:s 4, 5 and 6, wherein the sequence comprises the critical PYI motif.

This argument has been carefully considered, but is not found persuasive.

In response to Applicants argument that Maxwell fails to disclose the method set forth in the amended claims which relies on SEQ ID NO:s 4, 5 and 6, the Examiner recognizes that Maxwell et al. does not specifically teach the method requiring the amino acids consisting of SEQ ID NO: 4 or 5 or the oligonucleotide of SEQ ID NO: 6. However, the claims as currently amended do not appear to be solely drawn to SEQ ID NO:'s 4, 5 and 6. For example, the claims recite a method of evaluating an antagonist of the PYI motif **or** a protein encoded by one of SEQ ID NO:s 4,5 or 6 (emphasis added). Thus, as stated *supra* and admitted by Applicants, Maxwell teaches a method of evaluating a PYI antagonist.

New Objections:

Specification

The disclosure is objected to because of the following informalities: Page 1, line 4 recites "incline numberinglinecluding" which appears to be a typo.

Appropriate correction is required.

New Rejections necessitated by Amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, claim 40 is drawn to a method of evaluating an antagonist of the PYI motif or a protein encoded by one of SEQ ID NO:s 4, 5, or 6. However, the sequence represented as SEQ ID NO: 4 and 5 are amino acid sequences and not a nucleic acid sequence which encodes a protein. Thus, it is unclear what applicants are attempting to claim.

Claim 40 recites the limitation "said target protein" in claim 40. However, after careful review of the pending claims there does not appear to be a recitation of a target protein. As such, there is insufficient antecedent basis for this limitation in the claim. It is suggested that the limitation "target protein" be amended to recite the SEQ ID NO: 2.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Therefore, NO claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
3/1/06

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

POELLINGER et al

Application No.:	09/922,958	Art Unit:	1642
Filed:	August 7, 2001	Examiner:	Fetterolf, B. J.

Title: MECHANISM OF CONDITIONAL REGULATION OF THE HYPOXIA-INDUCIBLE FACTOR-1 BY THE VON HIPPEL-LINDAU-TUMOR SUPPRESSOR PROTEIN

AMENDMENT

Commissioner for Patents
PO BOX 1450
Alexandria, Virginia 22313
Via facsimile to 571 273 8300

Sir:

Applicants present the following amendments and arguments in response to the outstanding action mailed on March 3, 2006.

Certificate of Transmission
I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office (Fax. No. 571 273 8300) on July 6, 2006.

Signature Lena Hamber
Lena Hamber

REQUEST FOR EXTENSION OF TIME:

Applicants hereby request a two month extension to respond to the outstanding action. The fee for extension may be debited from Deposit Account No 501249.

AMENDMENTS TO THE SPECIFICATION:

Please amend paragraph 0001 of the application as follows:

[0001] The von Hippel-Lindau (VHL) disease is caused by germ line mutations of the VHL susceptibility gene. These mutations lead to the development of a variety of tumors ~~inline numberinglinecluding~~ including clear cell carcinomas of the kidney, pheochromocytomas and vascular tumors of the central nervous system and retina (Maher, E. R. et al., Medicine, 76:381-391, 1997; Kaelin, W. G. et al., Trends Genet., 14:423-426, 1998). Functional inactivation of both VHL alleles has been documented in a majority of sporadic clear cell renal carcinomas (Gnarra, J. R. et al., Nat. Genet., 7:85-90, 1994). Furthermore, reintroduction of a wild-type but not mutant VHL cDNA into VHL (-/-) renal carcinoma cells suppresses their ability to form tumors in nude mouse xenograft assays (Iliopoulos, O. et al., Nat. Med., 1:822-826, 1995; Gnarra, J. R. et al., Proc. Natl. Acad. Sci., 93:10589-10594, 1996). VHL-associated neoplasms are typically hypervascular and overproduce angiogenic factors such as vascular endothelial growth factor (VEGF) (Takahashi, A. et al., Cancer Res., 54:4233-4237, 1994; Wizigmann-Voos, S. and Plate, K. H., Histol. Histopathol., 11:1049-1061, 1996). Moreover, it has been shown that hypoxia-inducible inducible mRNAs, including VEGF mRNA, are constitutively expressed under normoxic conditions in VHL-deficient cells (Gnarra, J. R. et al., Proc. Natl. Acad. Sci., 93:10589-10594, 1996; Iliopoulos, O. et al., Nat. Med., 1:822-826, 1995; Siemeister, G. et al., Cancer Res., 56:2299-2301, 1996). Reintroduction of VHL into VHL (-/-) renal carcinoma cells indicates that it functions as a negative regulator of VEGF mRNA levels by either post-transcriptional mechanisms (Gnarra, J. R. et al., Proc. Nati. Acad. Sci., 93:10589-10594, 1996; Iliopoulos, O. et al., Nat. Med., 1:822-826, 1995; Siemeister, G. et al., Cancer Res., 56:2299-2301, 1996) and/or transcriptional mechanisms (Mukhopadhyay, D. et al., Mol. Cell. Biol., 17:5629-5639, 1997).

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

Claim 1 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered PYI motif at residues 564-566.

Claim 2 (Withdrawn): The isolated polypeptide of claim 1, wherein residues 564-566 are replaced by DDD.

Claim 3 (Withdrawn): The isolated polypeptide of claim 1, wherein residues 564-566 are replaced by AAA.

Claim 4 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered P564 residue.

Claim 5 (Withdrawn): The isolated polypeptide of claim 4, wherein residue 564 is replaced by A.

Claim 6 (Withdrawn): The isolated polypeptide of claim 4, wherein residue 564 is replaced by H.

Claim 7 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered YI656-566 residue.

Claim 8 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered PM567-568 residue.

Claim 9 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered DDD569-571 residue.

Claim 10 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered K547 residue.

Claim 11 (Withdrawn): The isolated polypeptide of claim 10, wherein the amino acid at position 547 is replaced by R.

Claim 12 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered Y565 residue.

Claim 13 (Withdrawn): The isolated polypeptide of claim 12, wherein the amino acid at position 565 is replaced by G.

Claim 14 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered I566 residue.

Claim 15 (Withdrawn): The isolated polypeptide of claim 14, wherein the amino acid at position 566 is replaced by G.

Claim 16 (Withdrawn): An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered FQL 572-574 residue.

Claim 17 (Withdrawn): The isolated polypeptide of claim 16, wherein the amino acids at positions 572-574 are replaced by AQA.

Claim 18 (Withdrawn): An isolated nucleic acid molecule comprising a polynucleotide sequence which encodes the polypeptide of claim 1.

Claim 19 (Withdrawn): A vector comprising the nucleic acid molecule of claim 18 in operative association with at least one promoter.

Claim 20 (Withdrawn): A host cell transformed or transfected with the vector of claim 19.

Claim 21 (Withdrawn): A pharmaceutical composition comprising the isolated polypeptide of claim 1 and at least one pharmaceutical carrier or adjuvant.

Claim 22 (Withdrawn): The vector of claim 19, wherein the vector is a plasmid.

Claim 23 (Withdrawn): The vector of claim 19, wherein the vector is a viral vector.

Claim 24 (Withdrawn): The vector of claim 19, wherein the vector is a retroviral vector.

Claim 25 (Withdrawn): The host cell of claim 20, wherein the host cell is a prokaryotic cell.

Claim 26 (Withdrawn): The host cell of claim 25, wherein the host cell is a bacterial cell.

Claim 27 (Withdrawn): The host cell of claim 25, wherein the host cell is a eukaryotic cell.

Claim 28 (Withdrawn): The host cell of claim 25, wherein the host cell is a mammalian cell.

Claim 29 (Withdrawn): A method of making a protein or a functional fragment thereof, comprising: introducing a nucleic acid according to claim 18 into a host cell or cellular extract; incubating said host cell or cellular extract under conditions such that said nucleic acid is expressed as a transcript and said transcript is expressed as a translation product comprising said protein; and isolating said translation product.

Claim 30 (Withdrawn): An isolated protein or a functional fragment thereof made by the method of claim 29.

Claim 31 (Withdrawn): A method of producing an isolated degradation box protein, comprising: infecting, transforming, or transducing a host cell with an expression vector comprising the nucleic acid of SEQ ID NO:2; culturing said host cell; and removing the isolated protein from said host cell.

Claim 32 (Withdrawn): An isolated protein or a functional fragment thereof, made by the method of claim 31.

Claim 33 (Currently amended): A method of screening for an agent which modulates the function of a protein comprising the amino acid of SEQ ID NO:5, comprising:

incubating a mixture comprising:

an isolated protein comprising the amino acid of SEQ ID NO:4 with an altered PYI motif at residues 564-566;

the sequence of SEQ ID NO:2 or a fragment thereof comprising SEQ ID NO:5 or SEQ ID NO:6; and

a candidate agent under conditions whereby, but for the presence of said agent, said isolated protein mediates VHL-dependent degradation or physically interacts with VHL at a reference affinity;

detecting the binding affinity of said isolated protein to said target protein to determine an agent-biased affinity;

wherein a difference between said reference affinity and said agent-biased affinity indicates that said agent modulates the functional activity of said isolated protein to said sequence of SEQ ID NO:2 or a fragment thereof comprising SEQ ID NO:5 or SEQ ID NO:6.

Claim 34 (Cancelled): The method of claim 33 wherein the target protein is VHL or a fragment thereof.

Claim 35 (Original): The method of claim 33 wherein the incubation is at normoxia.

Claim 36 (Original): The method of claim 33 wherein the incubation is at hypoxia.

Claim 37 (Withdrawn): A method of evaluating a potential analog of the PYI motif or P564 spanning protein or a functional fragment thereof for VHL-HIF-1 alpha interaction modulating efficacy, comprising: determining a natural VHL-HIF-1 alpha interaction within a cell, a group of cells, or an organism; administering said potential analog to an equivalent test cell, group of cells, or organism; measuring the level of VHL-HIF-1 alpha interaction in said test cell, group of cells, or organism; and determining said potential analog is efficacious when the measured test level of

VHL-HIF-1 alpha interaction is equal to or greater than the natural level of VHL-HIF-1 alpha interaction.

38 (Withdrawn): The method of claim 37, wherein said test cell, group of cells, or organism are at normoxia.

Claim 39 (Withdrawn): The method of claim 37 wherein said test cell, group of cells, or organism are at hypoxia.

Claims 40-42 (Cancelled).

Claim 43 (Withdrawn): A method of regulating the HIF-1 alpha signaling pathway of a bioentity selected from the group consisting of a cell, group of cells and a living organism, comprising administering a substance selected from the group consisting of a PYI motif, a functional fragment of a PYI motif, an analog of a PYI motif, a P564 spanning protein, a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein to said cell, group of cells, or living organism.

Claim 44 (Withdrawn): A method of regulating the HIF-1 alpha signaling pathway of a bioentity selected from the group consisting of a cell, group of cells and a living organism, comprising administering an antagonist of a PYI motif or an antagonist of a P564 spanning protein to said cell, group of cells, or living organism.

Claim 45 (Withdrawn): A method of treating disease, comprising administering full length HIF-1 alpha or an analog thereof, said full length HIF-1 alpha or analog containing at least one mutation or modification of the PYI motif to a cell, a group of cells, or an organism.

Claim 46 (Withdrawn): The method of claim 45 wherein said disease is an ischemic condition.

Claim 47 (Withdrawn): The method of claim 46 wherein said ischemic condition is selected from the group consisting of: brain infarction, heart infarction, and circulatory disorder.

Claim 48 (Withdrawn): A method of treating a disease selected from the group consisting of cancer, hypertension, demyelinating disorders, diffuse proliferative glomerculonephritis, toxoplasmosis caused retinochorioidits, HIV caused Tat angiongenesis, HIV caused Kaposi's sarcoma, hepatitis caused inflammation, hepatitis caused angiogenesis, chronic ulceration, proliferative retinopathy, retina hemangioblastomas, neovascularization, arterial hypervascularization, sarcoidosis, bullous skin disease, vasculitis with angiogenesis, dermatomyositis with angiogenesis, polymyositis with angiogenesis rheumatoid arthritis, juvenile

osteoarthritis, polyarthritis, aneurysm and atheroma, comprising administering an antagonist of the PYI motif or P564 spanning protein or a functional fragment thereof to a cell, a group of cells, or an organism.

Claim 49 (Withdrawn): A method of treating disease, comprising administering an agonist of the PYI motif or P564 spanning protein or a functional fragment thereof to a cell, a group of cells, or an organism.

Claim 50 (Withdrawn): The method of claim 49, wherein said disease is selected from the group consisting of ischemia, brain infarction, heart infarction, and circulatory disorder.

Claim 51 (Withdrawn): A method of promoting conditions in an in vitro culture, comprising adding a substance selected from the group consisting of a constitutively active HIF-1 alpha mutant, a functional fragment of a constitutively active HIF-1 alpha mutant, an agonist of the PYI motif, and an agonist of the P564 spanning protein to the culture.

Claim 52 (Withdrawn): The method of claim 51 wherein the culture is used to sustain or grow neural stem cells.

Claim 53 (Withdrawn): A pharmaceutical composition comprising a substance selected from the group consisting of a PYI motif, a functional fragment of the PYI motif, an analog of the PYI motif, a P564 spanning protein and a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein, and at least one pharmaceutical carrier or adjuvant.

Claim 54 (Withdrawn): A pharmaceutical composition comprising an antagonist of the PYI motif or an antagonist of the P564 spanning protein, and at least one pharmaceutical carrier or adjuvant.

Claim 55 (Withdrawn): A method of regulating the function of a molecule selected from the group consisting of HIF-1 alpha, EPAS, and HIF-3alpha in a cell, a group of cells, or an organism, comprising administering to said cell, group of cells, or organism a substance selected from the group consisting of the PYI motif, a functional fragment of the PYI motif, an analog of the PYI motif, a P564 spanning protein, a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein to said cell, group of cells, or organism.

Claim 56 (Withdrawn): A method of regulating the function of a molecule selected from the group consisting of HIF-1 alpha, EPAS, and HIF-3alpha in a cell, a group

of cells, or an organism, comprising administering an antagonist to the PYI motif or an antagonist to the P564 spanning protein to said cell, group of cells, or organism.

Claim 57 (Withdrawn): A method of effecting degradation of a molecule selected from the group consisting of HIF-1 alpha, EPAS, and HIF-3alpha in a cell, a group of cells, or an organism, comprising administering a substance selected from the group consisting of the PYI motif, a functional fragment of the PYI motif, an analog of the PYI motif, a P564 spanning protein, a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein to said cell, group of cells, or organism.

Claim 58 (Withdrawn): A method of increasing angiogenesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

Claim 59 (Withdrawn): A method of regulating angiogenesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

Claim 60 (Withdrawn): A method of increasing erythropoiesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

Claim 61 (Withdrawn): A method of regulating erythropoiesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

Claim 62 (Withdrawn): A method of controlling oxygen-dependent degradation of a protein, comprising incorporating the sequence of SEQ ID NO:5 in a cellular protein.

Claim 63 (Withdrawn): The method of claim 62 wherein said protein is GAL-4.

Claim 64 (Withdrawn): A method of detecting an HIF-1 alpha sequence encoding an oxygen-independent degradable HIF-1 alpha mutant, comprising evaluating of a sample sequence for an alteration to any one of residues 532 through 585.

Claim 65 (Withdrawn): The method of claim 64, wherein said alteration occurs to a residues selected from the group consisting of K547, P564, Y565, I566, P567, M568, D569, D570, D571, F572, Q573 and L574.

Claim 66 (Withdrawn): The method of claim 64, wherein said evaluation is effected by means selected from the group consisting of oligonucleotide probes, PCR-based diagnosis and antibodies.

REMARKS

In view of the foregoing amendments the Examiner is respectfully requested to reconsider and withdraw the outstanding objections and rejections.

Claims 33 and 35-36 stand rejected under 35 U.S.C. §112, first paragraph, for failure to comply with the written description requirement. In view of the present amendments, this rejection is respectfully traversed. The claimed invention relates to SED ID NO:2 and specific fragments thereof, namely, SEQ ID NO:s 5 and 6. As all sequences were present in the original text and their use in the claimed manner is supported by the description, withdrawal of the rejection is in order.

Claims 40-42 have been cancelled.

The Specification was objected to because of a typographical error on page 1, line 4. The same has been corrected herein.

Further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned.

Respectfully Submitted,

July 6, 2006

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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

30/8/06 Exist 30/11/06 308

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/922,958	**Applicant(s)** POELLINGER ET AL.
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *33,35,36 and 40-42*.
   Claim(s) withdrawn from consideration: *1-32, 37-39 and 43-66*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 07/06/2006 in response to the previous Final Office Action (03/03/2006) is acknowledged, but has not been entered because entry of the amendment would result in a new search of the prior art, with respect to SEQ ID NO: 5 and 6, as well as, new grounds of rejection under 112 1st paragraph, New Matter and 112, 2nd paragraph.

Claims 1-33 and 35-66 are currently pending

Claims 1-32, 37-39 and 43-66 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 33, 35-36 and 40-42 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-42 **remain** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, claim 40 is drawn to a method of evaluating an antagonist of the PYI motif or a protein encoded by one of SEQ ID NO:s 4, 5, or 6. However, the sequence represented as SEQ ID NO: 4 and 5 are amino acid sequences and not a nucleic acid sequence which encodes a protein. Thus, it is unclear what applicants are attempting to claim.

Claim 40 recites the limitation "said target protein" in claim 40. However, after careful review of the pending claims there does not appear to be a recitation of a target protein. As such,

there is insufficient antecedent basis for this limitation in the claim. It is suggested that the limitation "target protein" be amended to recite the SEQ ID NO: 2.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33 and 35-36 **remain** rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As set forth previously, "an isolated protein according to claim 29" is the isolated polypeptide of Claim 1 comprising an amino acid sequence of SEQ ID NO: 4 and fragments thereof with an altered PYI motif at residues 564-566. In the instant case, claims 33-36 are inclusive of a genus of molecules identified as comprising an amino acid sequence set forth in SEQ ID NO: 4 or any fragments and/or mutants thereof that bind to a genus of target proteins and fragments thereof referred to as "VHL". While claims 40-42 are inclusive of a genus of molecules referred to as having a "PYI motif" or functional fragments thereof and a genus of molecules referred to as "P564 spanning protein" or functional fragments thereof. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for methods of identifying agents.

The specification teaches (page 9, paragraph 0026-0027) that methods for identifying agents of the present invention includes, but is not limited to, polypeptides having at least an amino acid of SEQ ID NO: 5 (minimum N-TAD) or a smaller fragment thereof, SEQ ID NO: 6 (residues 547-575), or described mutants thereof and the VHL protein (SEQ ID NO: 2). With regards to the mutants, the specification teaches (Pages 6-7) that the mutants comprise altered amino acid residues such as; an altered PYI motif at residues 564-566, a ^{564}P, a $^{565\text{-}566}$YI, ^{565}Y, a $^{569\text{-}571}$DDD, ... ect.. The specification further teaches (page 13, paragraph 0042) that additional methods for identifying agents of the invention include, but are not limited to, polypeptides comprising a PYI motif or p564

spanning polypeptide (residues 547-575) or portion thereof. Thus, it appears that a p564 spanning polypeptide consists of the same amino acids as disclosed for SEQ ID NO: 6. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for identifying agents. Therefore, the written description does not commensurate with the full scope of any fragments and/or variants of SEQ ID NO: 4 or any fragments of the VHL protein (SEQ ID NO: 2).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of molecules that bind VHL nor does it provide a description of structural features that are common to SEQ ID NO: 4. Further, the specification fails to provide a representative number of molecules referred to as VHL along with a description of structural features that are common to the VHL. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of all the

fragments of SEQ ID NO: 4 and VHL, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a VHL protein (SEQ ID NO: 2) and two fragments of SEQ ID NO: 4,(SEQ ID NOs: 5 and 6), which comprise the PYI motif and p564 spanning protein, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In response to the rejection, Applicants contend that the claims have been amended which are believed to obviate this rejection. Specifically, Applicants assert that the claimed invention relates to SEQ ID NO: 2 and specific fragments thereof, namely SEQ ID NO: 5 and 6.

As, Applicant's arguments appear to be solely drawn to the claims as presently amended, but not entered, such arguments have not been considered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40-42 remain rejected under 35 U.S.C. 102(b) as being anticipated by Maxwell et al. (Nature 1999; 399: 271-275, IDS).

Maxwell discloses a method of evaluating an antagonist of the PYI motif for VHL-HIF-1 alpha interacting inhibiting efficacy; comprising: determining a reference level of VHL-HIF-1 alpha

interacting in a cell or group of cells; administering said antagonist to an equivalent test cell; measuring the level of VHL-HIF-1 alpha interaction in said test cell; and determining said antagonist is efficacious when the measured test level of VHL-HIF-1 alpha interaction is less than the reference level of VHL-HIF-1 alpha interaction (page 273, 1st column, 1st full paragraph to 2nd column). The reference further teaches that the test were done at both normoxic and hypoxic conditions (page 273, 1st column, 1st full paragraph to 2nd column). Thus, while the Maxwell et al. does not specifically state that the inhibitor is an agonist of the PYI motif, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Tanimoto et al. (EMBO 2000; 19: 4298-4309, IDS), the highly conserved core motif, i.e. PYI, of the N-TAD of HIF-1 alpha is critical for interaction with VHL (specifically page 4303, 1st column, 1st full paragraph). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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